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Terms for the Quantitation of a Mixture of Stereoisomers

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Abstract Various terms for the quantitation of a mixture of enantiomers and diastereomers are discussed.

Keywords Diastereomeric excess · Diastereomeric ratio · Enantiomeric composition · Enantiomeric excess · Enantiomeric fraction · Enantiomeric proportion · Enantiomeric ratio · Retention excess · Stereoselectivity factor

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1 Introduction

The enantiomeric proportion of macroscopic samples of chiral compounds requires its own descriptive adjectives [1]. The proposed terms should generally be applicable and suitable for two important borderline cases in enantiomeric analyses: (1) to establish the high enantiomeric purity status of natural compounds [2] and to determine minute amounts of enantiomeric impurities, e.g., in the evaluation of the enantioselectivity of enzymes and chiral catalysts in enantioselective syntheses and kinetic resolutions and (2) to determine low enantiomeric imbalances [3], e.g., minuscule deviations from truly racemic compositions in experiments devoted to the amplification of enantiomeric bias under prebiotic conditions.

The historical development of expressions for the quantitation of stereoisomeric proportions is outlined and recommendations for its contemporary use are presented. The stereoisomers are treated separately as enantiomers and diastereomers.

2 Enantiomers

Depending on whether a mixture of enantiomers is quantified by (1) spectroscopic or chromatographic methods, employing a nonracemic auxiliary compound, or by (2) chiroptical methods, different definitions have been used [4–10].

2.1 Nonchiroptical Methods

2.1.1 Enantiomeric Excess ee

Enantiomeric excess, ee, has been defined as the excess of one enantiomer over the other [1]. The expression ee was proposed in 1971 by Morrison and Mosher [5]:

$$\mathrm{ee} = (E_1 - E_2)/(E_1 + E_2), \tag{1}$$

where E_1 is the amount of the major enantiomer and E_2 is the amount of the minor enantiomer. The magnitude of the enantiomeric excess ee extends from ee = 0 for the racemic mixture to ee = 1 for pure E_1. The term ee is unequivocal, since it describes the relationship between two enantiomers in a mixture, as determined by whatever means are available [11]. Equation (1) was originally introduced by Raban and Mislow and was referred to as enantiomeric purity [4]. The incentive for the new definition arose from the assumption of numeric equality between optical rotation and enantiomeric proportion in nonracemic mixtures [4, 5]. Indeed it was stated that the value of the enantiomeric purity is identical with the value of the optical purity [4]. This statement is valid only when ideal conditions prevail in

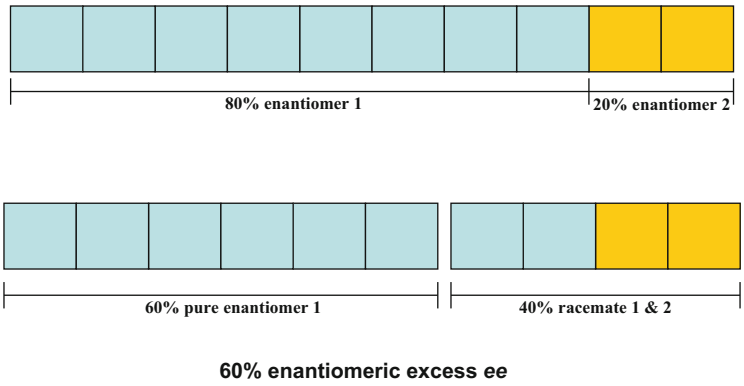

Fig. 1 Visualization of the definition of enantiomeric excess for ee = 60%

the determination of optical purity (see below). Moreover, the link to the criterion of purity in the terms enantiomeric purity and optical purity has subsequently been considered as unfortunate as it implies that the "impurity" is the racemic composition and not the minor enantiomer [11].

In practice, ee is often quoted as a percentage [1]:

$$\%\text{ee} = (E_1 - E_2)/(E_1 + E_2) \cdot 100 = \%E_1 - \%E_2. \tag{2}$$

The term ee has now correctly been defined as the excess of one enantiomer over the racemic composition in the mixture E_1 + E_2 [6, 12, 13]. Thus for a mixture of the proportion E_1:E_2 = 99:1, E_1 = 99% while ee = 98% and for a mixture enriched in one enantiomer, e.g., 80:20, E_1 = 80% but ee = 60% (Fig. 1).

When the mole or mass fractions x_{E1} and x_{E2} are used, the following simplified expressions apply because enantiomers possess the same molar mass and to due x_{E1} + x_{E2} = 1 [1]:

$$\text{ee} = x_{E1} - x_{E2} = 2x_{E1} - 1 = 1 - 2x_{E2} \tag{3}$$

The converse relations are [1]

$$x_{E1} = (1 + \text{ee})/2 \text{ and } x_{E2} = (1 - \text{ee})/2. \tag{4}$$

The expression *enantiomeric purity* was originally used as a synonym for ee [4]. However, the use of *enantiomeric purity* should be avoided as it has also been defined as mole fraction of the major enantiomer x_{E1} [4, 6] or simply as the percentage of one enantiomeric in a mixture [14, 15] (cf. the following section).

2.1.2 Enantiomeric Composition ec and Enantiomeric Fraction EF

The enantiomeric proportion of a sample may be described as the dimensionless mole ratio (or a mole percent of the major enantiomer) and this has been suggested the most generally useful way to describe the composition of all types of stereoisomeric mixtures [1]. The use of the mole fraction of the major enantiomer E_1 in a mixture, x_{E1}, was first suggested by Horeau (cf. footnote in [4]). It has been named *enantiomeric composition*, ec [8, 16]:

$$\text{ec} = x_{E1} = E_1/(E_1 + E_2). \tag{5}$$

The terms ec and ee are related as follows:

$$\text{ec} = \text{ee} + x_{E2} = (\text{ee} + 1)/2. \tag{6}$$

The *enantiomeric composition* of a sample has also been simply quoted as % E_1 and % E_2 [17].

More recently, the mole fraction of an enantiomer in a mixture is called *enantiomeric fraction* with the symbol EF_1 applying to the major enantiomer and EF_2 for the minor enantiomer [18–20]:

$$EF_1 = E_1/(E_1 + E_2) \text{ and } EF_2 = E_2/(E_1 + E_2). \tag{7}$$

The magnitude of the enantiomeric ratio EF extends from 0 to 1 with the value of 0.5 for the racemic mixture.

The enantiomeric ratio EF has now become the standard descriptor for chiral signatures of environmental samples [18]. The EF definition is superior because it provides meaningful representation of graphical data and is more easily employed in mathematical expressions of the fate of enantiomers in environmental compartments and for the investigation of enantioselective degradation processes [18] (Fig. 2).

2.1.3 Enantiomeric Ratio er and er_{inv}

The term *enantiomeric ratio*, er (ER or q), is defined as follows [8, 21–23]:

$$\text{er} = E_1/E_2, \tag{8}$$

where E_1 is the major enantiomer.

The magnitude of the enantiomeric ratio er extends from er = 1 for a racemic mixture to er = ∞ for pure E_1. Since er involves large numbers for the major enantiomer in high preponderance, the logarithmic scale, log er, extending from zero to infinity, has been proposed [24]. The terms er and ee are related as follows [8]:

$$\text{ee} = (\text{er} - 1)/(\text{er} + 1) \tag{9}$$

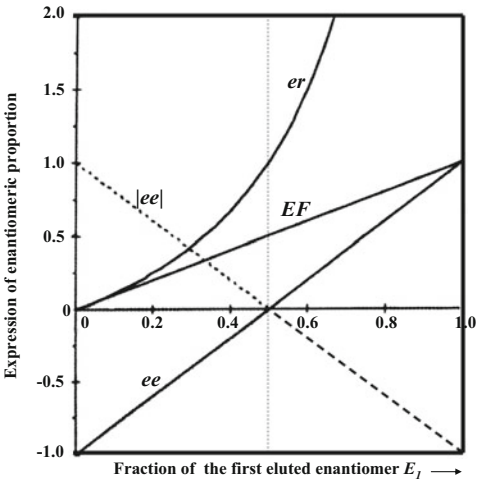

Fig. 2 Graphical representation of the various expressions for enantiomeric proportions plotted against the fraction of the first eluted enantiomer in enantioselective gas chromatography E_1 [19]. Reprinted with permission from [19], © Elsevier

and

$$\mathrm{er} = (1 + \mathrm{ee})/(1 - \mathrm{ee}). \tag{10}$$

The inverse definition of the enantiomeric ratio has also been considered [21, 22] and applied in practice [25]:

$$\mathrm{er_{inv}} = E_2/E_1 \tag{11}$$

$\mathrm{er_{inv}}$ and ee are related as follows:

$$\mathrm{er_{inv}} = (1 - \mathrm{ee})/(1 + \mathrm{ee}) \tag{12}$$

and

$$\mathrm{ee} = (\mathrm{er_{inv}} + 1)/(\mathrm{er_{inv}} - 1). \tag{13}$$

The magnitude of the inverse enantiomeric ratio $\mathrm{er_{inv}}$ extends from er = 0 for pure E_1 to $\mathrm{er_{inv}} = 1$ for a racemic mixture. Note that log $\mathrm{er_{inv}}$ is rendered negative.

2.1.4 Enantiomeric Ratio E and the Stereoselectivity Factor s in Kinetic Resolutions

A source of confusion associated with the term *enantiomeric ratio* has been addressed by Faber as the term is used in two different albeit related ways [26]. The enantiomeric ratio $\mathrm{er} = E_1/E_2$ is directly related to the ratio of the relative rate constants k_{E1}/k_{E2} in the conversion of prochiral substrates or in

meso-differentiating reactions whereby the ratio k_{E1}/k_{E2} is linked to the difference in the Gibbs free energy of activation of the diastereomeric transition states $\Delta\Delta G^{\#} = \Delta\Delta H^{\#} - T\Delta\Delta S^{\#} = -RT \ln er$. The ratio k_{E1}/k_{E2} is independent of the conversion of the reaction because the enantioselective transformations start with the same prochiral substrate S, i.e., $S \rightarrow E_1(k_{E1})$ and $S \rightarrow E_2(k_{E2})$. Therefore the ratio of the product enantiomers E_1 and E_2 will not change during the course of the reaction [26].

A more complicated situation arises in the realm of enzymatic kinetic resolution obeying Michaelis–Menton kinetics when the enantiomers E_1 and E_2 present in a sample are transformed at different rates to the enantiomeric products E'_1 and E'_2, i.e., $E_1 \rightarrow E'_1\,(k'_{E1})$ and $E_2 \rightarrow E'_2\,(k'_{E2})$. In the ideal case only E_1 is transformed to enantiopure E'_1 leaving enantiopure E_2 behind after 50% conversion c. In kinetic resolutions the rate of the reaction of E_1 and E_2 varies with the degree of conversion c since the ratio of the two enantiomers does not remain constant during the transformation. Furthermore, the enantiomeric excess of the substrates ee_S (E_1 and E_2) and of the products ee_P (E'_1 and E'_2) depends on the conversion c. Sih et al. arrived at a parameter describing the enantioselectivity of an irreversible enzymatic kinetic resolution devoid of product and substrate inhibition which is identical with the ratio of the rate constants (k'_{E1}/k'_{E2}) [27]. The parameter which remains constant during the kinetic resolution has been called the *enantiomeric ratio* E which is readily accessible from ee_S, ee_P, and c:

$$E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)] = k'_{E1}/k'_{E2} \tag{14}$$

with

$$c = 1 - (E_1 + E_2)/(E^{\circ}{}_1 + E^{\circ}{}_2) \tag{15}$$

When the product arising from the kinetic resolution is itself chiral the following expression can also be used [27, 28]:

$$E = \ln[1 - c(1+ee_P)]/\ln[1 - c(1-ee_P)] \tag{16}$$

A non-enantioselective kinetic transformation has an E value of 1 whereas an E value above 20 is the minimum for an acceptable kinetic resolution [29]. The enantiomeric ratio E is identical to the *stereoselectivity factor* s in the realm of general kinetic resolutions of racemic mixtures defined by Kagan and Fiaud and the same equations apply [30]. E is linked to the difference in Gibbs free activation energy difference of the diastereomeric transition states, i.e., $\Delta\Delta G^{\#} = \Delta\Delta H^{\#} - T\Delta\Delta S^{\#} = -RT \ln E$. An E value of 100 corresponds to $\Delta\Delta G^{\#}$ of 2.7 kcal/mol at 25 °C.

Equation (14) is rendered imprecise at very low or very high conversions c and it is preferentially used in the range of ~40–60% conversion to provide a substantial amount of chemical yield of both the product and the remaining substrate [26].

For low or high conversions c an equation was proposed which requires only the knowledge of ee_S and ee_P, being readily accessible by enantioselective NMR and enantioselective chromatography, whereby the conversion term c is substituted by $ee_S/(ee_S + ee_P)$ [31]:

$$E = [\ln[ee_P(1 - ee_S)]/(ee_P + ee_S)]/[\ln[ee_P(1 + ee_S)]/(ee_P + ee_S)] \quad (17)$$

or in its rearranged form [29]

$$E = \ln[(1 - ee_S)/(1 + (ee_S/ee_P)]/\ln[(1 + ee_S)/(1 + (ee_S/ee_P)] \quad (18)$$

E values greater than 200 should be treated with caution since small variations of ee_P and ee_S will cause large differences in the E value [26]. Reliable data for ee_P and ee_S ($ee > 99\%$) can be measured, e.g., by enantioselective gas chromatography [32].

2.1.5 Naming of Enantiomers: Eutomers and Distomers

The definition of an *enantiomer* [33] as one of a pair of molecules which are mirror images of each other and are non-superposable does not explicitly reserve specific names for the two distinct entities of stereoisomers (Greek: $\varepsilon\nu\alpha\nu\tau\acute{\iota}o\varsigma$ = *opposite* and $\mu\varepsilon\rho o\xi$ = part). This leads to undesired expressions in the literature such as the "wanted enantiomer" for the major enantiomer E_1 and the "wrong enantiomer" or "enantiomeric impurity" for the minor enantiomer E_2 in a mixture of high ee or er.

In pharmacology and pharmacy specific names have been introduced for a pair of enantiomers when a given biological system displays enantioselectivity. The more active enantiomer is termed the *eutomer* (Eu) and the less active enantiomer is called the *distomer* (Dis). The use of the terms derived from Greek $\varepsilon\upsilon$ = good, $\delta\upsilon\xi$ = bad, and $\mu\varepsilon\rho o\xi$ = part was suggested by Lehmann et al. [34] in analogy to the designations of *eutopic* (well-fitting) complexes and *dystopic* (ill-fitting) complexes [35]. A homologous series of enantiomeric pairs consist of a *eutomeric series* and a *distomeric series*. For a given enantiomeric pair the *ratio* of their activities is termed the *eudismic ratio* and its logarithm is termed the *eudismic index* (E.I.) [34, 36]. A correlation between the eudismic potency ratio and the averaged human potency of the racemate for 14 different drugs was discovered by Pfeiffer [37]. The generalized *Pfeiffer's rule* states that in a series of chiral compounds the *eudismic ratio* increases with increasing potency of the *eutomer*.

The definitions ee, er, and ec are derived with E_1 being the major enantiomer in a mixture, i.e., $x_{E1} > 0.5$. Unfortunately, in selected cases there is a need to cover the entire range of $0 \leq x_{E1} \leq 1$. Situations invoking opposite enantioselectivities are frequently encompassed in enzymatic reactions or in pharmacokinetic and pharmacodynamic studies of chiral drugs whereby opposite enantiomers may be favoured

Table 1 Comparison of the various definitions for the quantitation of a mixture of enantiomers

Enantiomeric proportion	% ec (EF)	% ee	er	log er	ln er
50:50	50	0	1	0	0
51:49	51	2	1.041	0.017	0.04
99:1	99	98	99	2	4.6
99.9:0.1	99.9	99.8	999	3	6.9
99.99:0.01	99.99	99.98	9,999	4	9.2
0.01:99.99	0.01	−99.98	0.0001	−4	−9.2

case by case. The different and opposite percentages of the enantiomers E_1 and E_2 are reflected in the definitions as characteristic, and sometimes negative quantities (ee). In the literature the total range $0 \leq x_{E1} \leq 1$ has been treated simply as a percentage, i.e., % E_1 and % E_2 [17], or by their ratio er [38]. Indeed, in cases where no emphasis is given to one major enantiomer, i.e., each of the enantiomers may be in preponderance at specific conditions, ee is not a useful term. The definitions EF and er or ln er are more appropriate in this circumstance (Table 1).

2.2 Chiroptical Methods

Historically, "optically active" has often been used as synonym for "chiral" and to describe nonracemic mixtures of enantiomers. This expression suffers from the fact that it is linked to the determination of chiroptical properties which is gradually being discontinued in modern methodologies to quantify enantiomeric proportions. Moreover, enantiomerically pure samples need not be optically active at a given concentration, temperature, wavelength, and solvent [39].

The term *optical purity* op (or *p*) is defined as the ratio of the measured specific rotation $[\alpha]$ of an enantiomeric mixture, divided by the maximum specific rotation $[\alpha_{max}]$ of one enantiomer (E_1 or E_2 with ee = 1) [4, 39]:

$$\text{op} = [\alpha]/[\alpha_{max}], \tag{19}$$

where the sign of the specific rotation and its complicated CGS dimension is ignored for convenience. In practice, op is quoted as a percentage:

$$\%\,\text{op} = [\alpha]/[\alpha_{max}] \cdot 100. \tag{20}$$

The specific rotation of a mixture of enantiomers is equal to the specific rotation of the pure enantiomer times the optical purity. These relationships are illustrated in Table 2 for a chiral compound whose maximum specific rotation $[\alpha_{max}]$ is arbitrarily set to 150 [6]. Knowing % op from polarimetric measurements one can calculate % E_1 and % E_2 [8]:

$$\%\ E_1 = (100 + \text{op})/2 \quad \text{and} \quad \%\ E_2 = (100 - \text{op})/2. \tag{21}$$

Table 2 Relationship between % enantiomeric proportion, % optical purity p, and specific rotation $[\alpha]$ [6]

Enantiomeric proportion %	% Optical purity	$[\alpha]$
100:0	100	+150
75:25	50	+75
50:50	0	0
75:25	50	−75
0:100	100	−150

Whereas the optical purity op relates to experimental properties, i.e., the specific rotations $[\alpha]$ and $[\alpha_{max}]$, the enantiomeric excess ee describes the composition of a chiral substance without recourse to any physical measurement [4]. Traditionally, op has been used for the quantitation of enantiomers because polarimetry had been the only tool available until the more recent advent of spectroscopic and chromatographic methods. However, op is related to experimental properties whose precision and accuracy is often unsatisfactory [12, 39].

The terms "non-racemic," "optically pure," and "enantiomerically enriched" imply that the racemate constitutes the impurity [14]. Both the definitions of op and ee account for this notion. Historically, the use of op and ee was also preferred since its numerical value is identical under ideal conditions. Thus in the absence of self-associations of enantiomers in non-ideal solutions, the measured optical purity op is equivalent to the value of the true enantiomeric excess ee:

$$\text{op} = [\alpha]/[\alpha_{max}] \equiv (E_1 - E_2)/(E_1 + E_2) = \text{ee}. \tag{22}$$

However, it is important to note that the measured optical purity op of a sample is not linearly related to the true enantiomeric excess ee when non-ideal conditions prevail in concentrated solutions, i.e., when the enantiomers interact between themselves. Thus, the op may markedly deviate from the true ee if the enantiomers undergo molecular self-association to dimers and/or oligomers. The associates formed in solution will display their individual optical rotation and, depending on their concentration, contribute in a specific way to the overall specific rotation. The non-equivalence between op and ee has been experimentally demonstrated for 2-ethyl-2-methylbutanedioic acid in dichloromethane by Horeau (the "Horeau effect," Fig. 3) [40].

The mole fractions of x_{E1} and x_{E2} of enantiomers present in a mixture can be calculated from the measured op [8]:

$$x_{E1} = (1 + \text{op})/2 \tag{23}$$

and

$$x_{E2} = (1 - \text{op})/2. \tag{24}$$

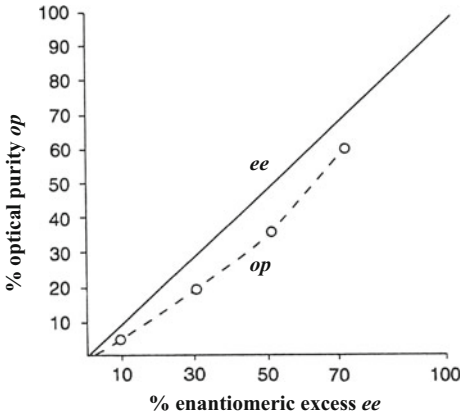

Fig. 3 Non-equivalence between optical purity % op and enantiomeric excess % ee for 2-ethyl-2-methylbutanedioic acid in dichloromethane [40]. Reprinted with permission from [40], © Elsevier

The prerequisite for determining op is a moderate-to-high value of the specific rotation of the sample permitting the correct determination of small differences of the op. Specific rotations may vary from very high values, e.g., for helicenes, to very low values, e.g., for unfunctionalized saturated hydrocarbons. The individual contributions of different elements of chirality (including induced chirality) in a molecule may also lead to an accidental cancellation of the optical activity. Another cause of apparent optical inactivity is the change of the sign of the ORD (optical rotatory dispersion) curve at a specific wavelength.

It has been remarked that measurements of optical rotations is assumed by many chemist to be a trivial experimental procedure because the basic instrument is relatively simple and adaptable in undergraduate laboratories [39]. The fact is, however, that optical rotations are not necessarily self-consistent because variations can occur with any of the parameters often assumed to be constant, i.e., temperature, concentration, wavelength, and solvent. In addition, parameters such as purity of the sample and solvent must be the same for the determination of $[\alpha]$ and $[\alpha_{max}]$. The maximum specific rotation $[\alpha_{max}]$ is not always known and it requires an independent proof of the 100% ee of the sample by a non-chiroptical method. The error due to the instrument reading becomes dramatic for samples with very low optical rotation and at nearly racemic compositions. The uncritical use of apparent values for $[\alpha_{max}]$ led to pitfalls in the optical purity determination of enantioselective transformations [7]. Thus the op of unreacted cycloolefin in the classical Brown kinetic resolution of 3-methylcyclopentene with (+)-diisopinocampheyl borane [41] was not 65% based on an erroneous experimental and theoretical value of $[\alpha_{max}]$ [42] but only 30% through evidence by enantioselective GC [43]. A serious source of error in determining op may arise from the concentration dependence of the specific rotation [39]. Examples are malic acid in water and 2-phenylpropanol in benzene [7]. Thus the op of hydratropaldehyde (2-phenylpropanal) obtained by hydroformylation of styrene had to be corrected from 95 to 73% when specific rotations were re-measured under identical conditions (solvent, concentration, temperature) [44].

The claim of enantiomeric bias via asymmetric synthesis in a rapidly spinning reaction vessel by employing the chiral gravitational field on Earth [45], later disputed on theoretical grounds [46], was solely based on minute (a few millidegrees) optical rotations. Values for op $> 97\%$ may be questionable unless experimental conditions are clearly stated and claims of op $= 100\%$ determined by polarimetry should be treated with the necessary caution.

The use of op has been gradually discontinued and the enantiomeric composition of a sample should only be linked to *optical purity* when exclusively chiroptical methods were employed. This applies, e.g., to chiroptical detectors in enantioselective liquid chromatography [47].

3 Selected Applications of the Terms ee, er, and ec (EF)

3.1 Enantiomeric Excess ee

Enantiomeric excess ee is compatible with the law of mixing (mixing of samples of different ee) and it is useful for calculating the corrected ee when auxiliary compounds with ee < 1 are used in enantioselective synthesis and catalysis [8]. When ee$^\circ$ refers to the maximum ee of the product with an enantiopure auxiliary, the expected ee_{prod} observed (in the absence of nonlinear effects) with an auxiliary of ee_{aux} is given by [8]

$$ee_{prod} = ee^\circ \cdot ee_{aux}. \tag{25}$$

In enantioselective chromatography the chiral selector employed is not always available in an enantiomerically pure form. However, the magnitude of the enantioseparation factor $\alpha = k_2/k_1$, i.e., the ratio of the retention factors of the enantiomers, critically depends on the enantiomeric excess ee of the chiral selector. The value of the maximum enantioseparation factor $\alpha^{ee=1}$ of a chiral selectand which can be attained on a sometimes elusive enantiomerically pure selector with ee $= 1$ can be extrapolated from the enantioseparation factor α measured on an enantiomerically impure selector as follows [48, 49]:

$$\alpha^{ee=1} = [(\alpha + 1)ee + (\alpha - 1)]/[(\alpha + 1)ee - (\alpha - 1)]. \tag{26}$$

An equation describing the drop of α with decreasing ee of a chiral selector can be obtained by rearranging (26) or can be derived de novo by independent considerations [50], including a virtual tandem column approach for which the definition of ee is mandatory [51, 52]:

$$\alpha^{obs} = \left[\alpha^{ee=1}(1 + ee) + (1 - ee)\right]/\left[\alpha^{ee=1}(1 - ee) + (1 + ee)\right]. \tag{27}$$

Thus an enantioseparation factor of $\alpha^{ee=1} = 100$ achieved on an enantiomerically pure selector (ee = 1) drops by more than half to $\alpha^{obs} = 49.75$ when the selector contains as little as 1% of an enantiomeric impurity (ee = 0.98) [50, 51, 53]! The large drop of the enantioseparation factor α of a racemic selectand with decreasing ee of the selector is due to the definition of selectivity as the ratio between retention factors with α resembling the term er. In order to get the same graphic relationship between ee of catalysts and ee of product enantiomers employed in enantioselective catalysis (Fig. 4), the definition *retention excess* re has been introduced in enantioselective chromatography [50, 52] where k_2 and k_1 are the retention factors of the second and first eluted enantiomers, respectively:

$$\text{re} = (k_2 - k_1)/(k_1 + k_2). \tag{28}$$

The retention excess re and the enantioseparation factor α are related to each other by the following expressions:

$$\text{re} = (\alpha - 1)/(\alpha + 1) \quad \text{or} \quad \alpha = (1 + \text{re})/(1 - \text{re}). \tag{29}$$

The unified linear correlation between ee of chiral catalysts in enantioselective catalysis and ee of selector in enantioselective chromatography toward ee of major product enantiomer and re of separated enantiomers, respectively is depicted in Fig. 4.

The term re has also been linked to an *enantioselectivity scale ESS* which defines the ability of an enantiopure chiral selector to produce a retention excess re for the enantioseparated selectands, i.e., re = ESS = 1 refers to 100% enantioselectivity with $\alpha = \infty$, whereas re = ESS = 0.5 refers to 50% enantioselectivity producing $\alpha = 3$ and re = ESS = 0 refers to nil enantioselectivity with $\alpha = 1$ [52]. The unified definition ESS applies both to a chiral catalyst in enantioselective catalysis and to a chiral selector in enantioselective chromatography (Fig. 4). For example, the major enantiomer with ee = 0.5 obtained by enantioselective catalysis (kinetic control) and the enantiomers with re = 0.5 separated by enantioselective chromatography (thermodynamic control) results either from enantiomerically pure auxiliaries with ee = 1 and ESS = 0.5 or from enantiomerically impure auxiliaries with ee = 0.5 and ESS = 1 (Fig. 4) [52].

3.2 Enantiomeric Composition ec and Enantiomeric Fraction EF

The enantiomeric fraction EF is based on a bounded additive scale that is linear and finite ranging from 0 to 1 and is symmetric about the equivalency value EF = 0.5 for the racemic composition (Fig. 2) [54]. DeGeus et al. argue that enantiomeric differences in a number of experimental data may either be overestimated for ER (er or q) values larger than unity or underestimated for ER values smaller than unity due to the nonlinear scale of the multiplicative ER definition (Fig. 2) leading to

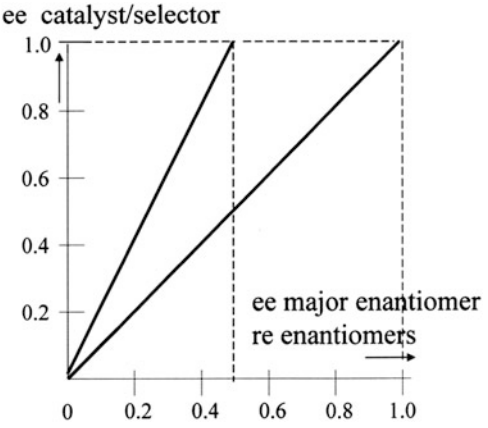

Fig. 4 Unified linear dependence of ee of chiral catalysts and ee of chiral selector with ee of major product enantiomer and re of selectand enantiomers for 50% and 100% enantioselectivity (ESS = 0.5 and ESS = 1), respectively [52]. Reprinted with permission from [52], © Elsevier

skewed data distributions, whereas the linearity of the EF scale (Fig. 2) causes changes to be numerically the same both above and below the 0.5 value for the racemic composition [19].

3.3 *Enantiomeric Ratio er and er_{inv}*

For the quantitative differentiation of enantiomers by enantioselective NMR and chromatography, the enantiomeric ratio er is directly obtained by peak integration of non-equivalent resonances in the NMR spectra and of enantioseparated peaks in the chromatograms. Thus cumbersome re-calculation in the ee scale is not required. The er is compatible with Hammett or Eyring relationships [8] and is a direct measure of the kinetic ratio k_{Re}/k_{Si} in enantiotopos- and enantiofacial-differentiating enantioselective reactions [8, 11, 21]. The Gibbs free energy difference of diastereomeric transition states is $\Delta\Delta G^{\#} = \Delta\Delta H^{\#} - T\Delta\Delta S^{\#} = -RT$ ln er. An er value of 99 corresponds to $\Delta\Delta G^{\#}$ of 2.7 kcal/mole at 25°C. Thus this rather small energy difference already produces enantiomers in the proportion of E_1:E_2 = 99:1. Selke et al. prefer the definition er for the comparison of two different asymmetric hydrogenations employing distinct catalysts by introducing the relative enantioselectivity factor Q [21, 22]. The following equation allows the calculation of the expected enantiomeric ratio er_2 of a de novo catalyst from Q and er_1 of the first catalyst:

$$er_2 = Q \cdot er_1. \tag{30}$$

The term er is the expression of choice in the realm of very high enantiomeric ratios since very large differences between the proportions of enantiomers are not properly represented by the ee definition close at unity. Thus, EF and er or ln er may eventually supersede the more traditional term ee.

In enantioselective chromatography, the enantiomer of opposite configuration has been used as an ideal internal standard for the quantitation of the target enantiomer in a mixture, provided that self-recognition of enantiomers in concentrated solutions is absent. The approach called *enantiomer labeling* [55] is intriguing because enantiomers possess identical non-chiroptical properties in an achiral environment and therefore the enantiomeric composition is not influenced by sample manipulation (isolation, derivatization, fractionation, storage), by chromatographic manipulations (dilution, partitioning, splitting, injection, detection), or by losses (thermal or catalytic decomposition and incomplete isolation). The inverse enantiomeric ratios er_{inv} of sample and standard are used by the "enantiomer labeling method" when sample and standard are not enantiomerically pure. The amount of the chiral component in a sample X after addition of the chiral standard is obtained as follows [55]:

$$X = m_S[(A_R - A_S \cdot er_{invS})(1 + er_{invR})/(A_S - A_R \cdot er_{invR})(1 + er_{invS})], \qquad (31)$$

Where A_R = peak area of the (*R*)-enantiomer after addition of the standard, A_S = peak area of the (*S*)-enantiomer after addition of the standard, er_{invR} = inverse enantiomeric ratio (*S*)/(*R*) of the sample, er_{invS} = inverse enantiomeric ratio (*R*)/(*S*) of the standard, m_S = amount of enantiomeric standard (*S*) added, and X = amount of the chiral component (as sum of its enantiomers) present in the sample.

4 Recommendations for the Quantitation of a Mixture of Enantiomers

The enantiomers present in unequal amounts in a mixture are called the *major enantiomer* E_1 and the *minor enantiomer* E_2.

The *enantiomeric excess* ee, *enantiomeric ratio* er or ln er, and *enantiomeric composition* ec *or* EF are useful terms for the quantitation of a mixture of enantiomers. Each term has its merits under special circumstances. The enantiomeric ratio er is the best descriptor for the result of enantioselection of enantiotopic faces or enantiotopic atoms or groups in a prochiral substrate. Enantioselectivity is reflected by the ratio of products since the relative rates of reaction determine the product ratio by kinetic control [11]. The recommendation to discontinue or prohibit the use of ee [11] is not justified.

For synthetic kinetic resolutions the stereoselectivity factor s is employed whereas for enzymatic kinetic resolutions the enantiomeric ratio E is used which must clearly be distinguished from the coequal term enantiomeric ratio er.

In studies on the fate of enantiomers in the environment or in biological matrices the term enantiomeric fraction EF should be used in lieu of the enantiomeric ratio previously expressed as the terms er and ER [54, 56] or er_{inv} [25].

Only % op is determined when chiroptical detectors are used in enantioselective liquid chromatography and % ee is equivalent to % op only in the absence of self-association of enantiomers.

For the sake of a unified terminology, the following expressions should be avoided, i.e., *enantiomeric yield* and *enantiomeric purity*, while the term *enantiomeric composition* must be correctly defined when applied, e.g., as a mole fraction of the major enantiomer x_{E1}.

It should be noted that the original proportions of the enantiomers in a sample may be altered by *accidental enrichment* during purifications, e.g., by crystallization or by chromatography [1, 12, 57]. Detailed information on sample preparation and analytical procedures are required when % ee = 100 (!) is claimed in enantioselective transformations.

The use of the term *homochiral* for % ee = 100 or, likewise, *heterochiral* for racemic (% ee = 0) should be discontinued [1, 58] since these terms have been reserved for other more concise meanings [59–61]. Eliel et al. proposed to use the expression "enantiomerically pure" (or the contraction "enantiopure") to describe enantiomerically homogeneous samples [62]. In accordance with common practice, the term *nonracemic* rather then *scalemic* [14, 16] is used as synonym of "enantiomerically enriched" and *enantiopure* rather than *holemic* [14] is used as synonym for "enantiomerically pure". As an alternative expression for the macroscopic single-enantiomeric composition the conceptual term *unichiral* has been proposed by Gal [63].

Optical purity op should only be referred to when non-chiroptical methods are not available for the quantitation of a mixture of enantiomers. The origin and reliability of $[\alpha]_{max}$, used for the calculation of op, should always be quoted.

Clearly, the prefix *optical* should never be used in connection with nonchiroptical methods (Sect. 2.1) and expressions such as *optical purity determination by NMR* or *optical resolution by chromatography* should be avoided.

Unfortunately, little attention has been focused in the literature on the nature and range of errors involved in the quantitation of a mixture of enantiomers. It is interesting to scrutinize how precision and accuracy will affect the definitions discussed herein. For example, ee is sensitive to an error in the percentage of the enantiomers, i.e., % (E_1:E_2 = 52 ± 1:48 ± 1) → % ee = 4 ± 2 [9]. De Geus et al. argue that relative standard deviations (RSD) derived from EF (ec)-based calculations are rendered only half as large as those obtained from er calculations [19]. Moreover, when for example a duplicate measurement is performed and the areas (in arbitrary units) are 12.5 and 10.0 in the first run, and 10.0 and 12.5 in the second, ERs of 12.5 and 0.80 results with the mean value of 1.02 instead of 1.00. The EFs calculated to 61% and 39% afford the correct mean value of 50% [19]. Applying parametric summary statistics, such as mean and standard deviation, to EF data is more appropriate because its additive scale provides data which are more symmetric than those obtained using the ER scale [19, 54].

5 Diastereomers

In analogy to the definitions for a mixture of enantiomers, the *diastereomeric excess* de:

$$\text{de} = D_1 - D_2/D_1 + D_2 \tag{32}$$

or the *diastereomeric ratio* dr (or q): [8]

$$\text{dr} = D_1/D_2 \tag{33}$$

have been used for the quantitation of a mixture of diastereomers in the case that only two isomers D_1 and D_2 are involved (this applies for epimers, anomers, and geometrical (*cis,trans*/*E,Z*/*syn,anti*/*endo,exo*)-isomers) where D_1 is the major diastereomer. Complications arise with the occurrence of stereoisomerism due to the presence of multiple stereogenic elements. Two distinct stereogenic elements in a molecule give rise to two diastereomers each forming a pair of enantiomers. When the stereoisomers are chiral and nonracemic, the definitions de and dr do not, a priori, differentiate between the proportions of the enantiomers, but treat them as the sum, i.e., $D_1 = E_1 + E_2$. Therefore, unless the proportions of all stereoisomers are preferably given as a percentage or as mole fraction, the mixture of enantiomers of each of the diastereomers must be quantified separately by ee or er.

Whereas dr is measured by spectroscopy or chromatography of diastereomers in an achiral environment, dr and er can be obtained simultaneously by employing enantioselective methods with appropriate chiral selectors.

When more than two diastereomers are involved, the term diastereoselectivity ds has been suggested as the mole fraction of diastereomer D_1 in a mixture of all diastereomers $\sum D_i$ [64]. In analogy to ec, this term is called *diastereomeric composition* dc

$$\text{dc} = x_{D1} = D_1/\Sigma D_i \tag{34}$$

The mole fraction of the major enantiomer x_{E1} of a chiral diastereomer D_i in a mixture of two or more diastereomers is given by

$$x^i_{E1} = \text{ec}^i \cdot \text{dc}^i. \tag{35}$$

The terms for diastereomers present in a mixture are summarized as follows:[9]

ee = enantiomeric excess
er = enantiomeric ratio
ec = enantiomeric composition
de = diastereomeric excess (for $\sum D_i = 2$)
dr = diastereomeric ratio (for $\sum D_i = 2$)
dc = diastereomeric composition (for $\sum D_i = 2$)

6 Recommendations for the Quantitation of a Mixture of Diastereomers

The use of the term *diastereomeric excess* % de is discouraged except for selected applications (see below). Seebach et al. argue that the commonly used % de is not a useful number because it is applicable to mixtures of two and only two diastereomers and because one has to convert it back to a diastereomeric ratio dr to arrive at a meaningful number (footnote 13 in [64]).

The term *diastereomeric ratio* dr or ln dr is useful for the quantitation of a mixture of two achiral or of two chiral (either racemic or enantiopure) diastereomers. When two or more chiral and nonracemic diastereomers *i* are present in a mixture, the proportions of the major diastereomer and major enantiomer are quantified by dc^i and ec^i. When all stereoisomers, i.e., diastereomers and enantiomers, are considered, their proportions are best quoted as mole fractions or percentages.

When the enantiomeric excess of a substrate $ee_{substrate}$ is determined via formation of diastereomers by achiral NMR spectroscopy or achiral chromatography the measured diastereomeric excess $de_{measured}$ must be corrected for the ee_{aux} of the auxiliary in case it is not enantiomerically pure [65]:

$$ee_{substrate} = de_{measured}/ee_{aux}. \tag{36}$$

Consider a substrate consisting of 90% E_1 and 10% E_2 ($ee_{substrate} = 0.80$) which is reacted with an auxiliary consisting of 95% E'_1 and 5% E'_2 ($ee_{aux} = 0.90$). Following quantitative derivatization four stereoisomers are present: $E_1E'_1 = 85.5\%$, $E_1E'_2 = 4.5\%$, $E_2E'_1 = 9.5\%$, and $E_2E'_2 = 0.5\%$. The mixture renders two signals or peaks of the diastereomers $E_1E'_1$ and $E_2E'_2$ (enantiomeric pair 1) and $E_1E'_2$ and $E_2E'_1$ (enantiomeric pair 2) with the proportion 86.0% and 14.0%, respectively, with $de_{measured} = 0.72$. The data is compatible with (36).

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